NON ENDOSCOPIC PREDICTORS OF OESOPHAGEAL VARICES IN PATIENTS WITH CIRRHOSIS OF THE LIVER

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CERTIFICATE

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DECLARATION

I solemnly declare that the dissertation entitled **"NON ENDOSCOPIC PREDICTORS OF OESOPHAGEAL VARICES IN PATIENTS WITH CIRRHOSIS OF THE LIVER"** is done by me at Madras Medical College and Hospital, during 2004-2006 under the guidance and supervision of **Prof.V.RAJI, M.D.** This dissertation is submitted to The Tamil Nadu Dr.M.G.R. Medical University towards the partial fulfilment of requirements for the award of **M.D. DEGREE IN GENERAL MEDICINE (BRANCH I)**.

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ABBREVIATIONS

ANOVA	-	Analysis of Variance
SPSS	-	Statistical package for social studies
ROC	-	Receiver operating characteristics
SAAG	-	Serum albumin-ascites gradient
GI	-	Gastrointestinal
USG	-	Ultrasonogram

INTRODUCTION

Portal hypertension is the consequence of an increase in the splanchnic blood flow secondary to vasodilation and increased resistance to the passage of blood through the cirrhotic liver[1]. Development of oesophageal varices is one of the major complications of portal hypertension[2]. Its prevalence varices from 50-60% in patients with cirrhosis of the liver[3]. After varices have developed, about one-third of patients die of bleeding gastro-oesophageal varices[4]. The risk of initial bleeding from varices is 25-35% within two years with most first bleeding episodes occurring within one year after detection of varices[5]. The reported mortality from first episode of variceal bleeding ranges from 40-70%.

In 1996, The American Association for the study of liver disease stated that all cirrhotic patients should be screened for the presence of oesophageal varices when portal hypertension is diagnosed. Recently, the Baveno III consensus conference on portal hypertension recommended that all cirrhotic patients should be screened for the presence of oesophageal varices when liver cirrhosis is diagnosed[6]. Repeat endoscopy is recommended at 2-3 years intervals in patients without varices and at 1-2 years interval in patients with small varices to evaluate the development or progression of varices[7].

However, this approach has two major limitations. Endoscopy is an invasive procedure and secondly the cost effectiveness of this approach is also questionable[8], as only 9-36% patients with cirrhosis are found to have varices on screening endoscopy. It may therefore be more cost effective to routinely screen patients at high risk for the presence of varices, so as to reduce the increasing burden and procedure costs of endoscopy units. Certain biochemical, clinical and ultrasonographic parameters alone or together have good predictive power for non-invasively assessing the risk of bleeding from varices. However, the factors that predict the presence of varices are not as well-defined. Identification of non-invasive predictors of oesophageal varices will enable us to carry out upper GI endoscopy in selected groups of patients, thus avoiding unnecessary intervention and at the same time not missing the patients at risk of bleeding.

AIM OF THE STUDY

- To identify the clinical, biochemical, haematological and ultrasonographic parameters associated with presence of oesophageal varices in patients with cirrhosis of liver without any previous evidence of GI bleeding.

- To assess the ability of these parameters as non invasive tools to predict the presence of oesophageal varices.

- To identify candidates for surveillance endoscopy based on the presence of these parameters.

MATERIALS AND METHODS

Study design: Prospective, cross-sectional, randomised analysis study.

The study was carried out at the Institute of Internal medicine, Government General, Hospital, Chennai from January 2004 to January 2006.

Inclusion criteria were as follows

- Patients with cirrhosis of liver without any past history of upper (or) lower gastrointestinal bleed were included in the study.
- Diagnosis of cirrhosis was based on a combination of physical findings when present like Gynaecomastia, Ascites, splenomegaly (etc), impaired liver function tests (ie) deranged clotting profile and low serum albumin and irregular liver surface with coarse echoes (or) shrunken liver and ratio of transverse caudate lobe to transverse right lobe width >0.65[9] an ultrasonographic examination.

Exclusion criteria were as follows

- Patients with present or previous history of bleed.
- Patients on previous/current treatment with Beta blockers, Diuretics (or) anti-platelet drugs.
- Patients who had undergone sclerosis (or) band ligation of oesophageal varices, TIPSS (or) surgery for portal hypertension.

- Active alcohol abuse (less than six months abstinence)
- Patients with serum albumin <1.5 gm

All patients included in the study were subjected to detailed history, clinical examination and blood investigations. Clinical examination of the study population was concentrated on the physical findings in cirrhotic patients, and special emphasis was on the presence of a palpable spleen. Other features like Jaundice, Gynaecomastia, spider naevi, Hepatic flap and Ascites were also noted.

Routine blood investigations like Blood urea, sugar serum creatinine and serum electrolytes were taken along with blood for hepatitis serology and liver function tests. Platelet count was estimated using automated analyser (sysmex KX-21). Hepatitis B surface antigen and anti-HCV antibody were investigated in all blood samples. Liver function tests were done and included SGOT, SGPT, Alkaline phosphatase, serum albumin and Serum-Bilirubin. The prothrombin time was also estimated for all the patients. All patients in the study group were classified into child's grade A/B/C based on child-pugh criteria[10,11].

Chest X-ray and ECG were taken for all patients. In addition, all the patients were subjected to ultrasonographic examination to assess the liver size, structure and the size of the portal vein, and size of spleen. A 3.5MHZ transducer was used for USG study.

All patients underwent upper GI endoscopy to evaluate for the presence of and the degree of oesophageal varices. Oesophageal varices were classified into small and large varices based on the following findings.

- Small oesophageal varices were defined as those that flatten with insufflation or minimally protrude into the oesophageal lumen.

- Large varices were defined as those which protrude into the oesophageal lumen and touch each other (or) fill at least 50% of the oesophageal lumen[12].

REVIEW OF LITERATURE

Cirrhosis is a pathologically defined entity that is associated with a spectrum of characteristic clinical manifestations. The cardinal pathologic features reflect irreversible chronic injury of the hepatic parenchyma and extensive fibrosis in association with the formation of regenerative nodules.

CLINICAL FEATURES OF HEPATIC CIRRHOSIS

- Hepatomegaly (although liver may also be small)
- Jaundice
- Ascites
- Circulatory changes
    - ♦ Spider telangiectasia, palmar erythema, cyanosis
- Endocrine changes
    - ♦ Loss of libido, hair loss
    - ♦ Men: gynaecomastia, testicular atrophy, impotence
    - ♦ Women: breast atrophy, irregular menses, amenorrhoea
- Hemorrhagic tendencies
    - ♦ Bruises, purpura, epistaxis, menorrhagia

- Portal hypertension
    - ♦ Splenomegaly, collateral vessels, variceal bleeding, fetor hepaticus
- Hepatic (portosystemic) encephalopathy
- Other features
    - ♦ Pigmentation, digital clubbing, low-grade fever

Child-pugh classification of prognosis in cirrhosis

Score	1	2	3
Encephalopathy	None	Mild	Marked
Bilirubin (mol/L)	<34	<34-50	>50
Albumin (g/L)	>35	28-35	<28
Prothrombin time (seconds prolonged)	<4	4-6	>6
Ascites	None	Mild	Marked
Add the indvidual scores: <7=Childs'A 7-9=Childs'B >9=Childs'C			

SURVIVAL IN CIRRHOSIS

Child-pugh grade	Survival (%)			Hepatic deaths (%)
	1 year	5 years	10 years	
A	82	45	25	43
B	62	20	70	72
C	42	20	0	85

PROGNOSIS

The overall prognosis in cirrhosis is poor. Many patients present with advanced disease and/or serious complications that carry a high mortality. Overall, only 25% of patients survive 5 years from diagnosis but, where liver function is good, 50% survive for 5 years and 25% for upto 10 years. The prognosis is more favourable where the underlying cause of the cirrhosis can be corrected, as in alcohol misuse, haemochromatosis and Wilson's disease.

Laboratory tests give only a rough guide to prognosis in individual patients. Deteriorating liver function, as evidenced by jaundice, ascites or encephalopathy, indicates a poor prognosis unless a treatable cause such as infection is found. Increasing plasma bilirubin, falling plasma albumin or an albumin concentration <30 g/L, marked hyponatraemia (<120mmol/L not due to diuretic therapy) and a prolonged prothrombin time are all bad prognostic signs. The course of cirrhosis is uncertain, as unforeseen complications such as variceal bleeding may lead to death unexpectedly.

PORTAL HYPERTENSION

Portal hypertension is one of the prime complications of cirrhosis. Patients developing clinical features or complications of cirrhosis usually have portal venous pressures above 12 mmHg.

COMPLICATIONS OF PORTAL HYPERTENSION

1. Variceal bleeding
2. Congestive gastropathy
3. Hypersplenism

4. Ascites
5. Renal failure
6. Hepatic encephalopathy

PATHOPHYSIOLOGY OF PORTAL HYPERTENSION

Normal Physiology

The movement of portal blood across the liver is dependent on the pressure gradient between the portal and hepatic veins[13]. Hepatic venous pressure in part reflects the state of central venous filling pressure. Portal pressure is determined by the product of portal venous inflow and the vascular resistance of this flow:

Portal pressure = portal flow x vascular resistance

Normally, the difference between portal venous pressure and hepatic venous pressure is never greater than 4mm Hg. A compliant liver acts as a blood reservoir to maintain a normal hepatic pressure gradient[14]. When outflow pressure increases, an increasing number of sinusoids are recruited to accommodate these changes. Thus, elevations of hepatic venous pressures do not result in similar increases in portal pressure.

The main site of portal vascular resistance in humans appears to reside at the level of the hepatic sinusoids[15].

Portal venous inflow is the sum of the flows from the 3 main splanchnic tributaries[16]. The splenic vein joins the inferior mesenteric vein at the level of the

pancreatic body and tail, where pancreaticoduodenal vessels also enter. Superior mesenteric venous drainage from the small and proximal large intestine joins the splenic vein at a site superior to the pancreatic head, forming the portal vein trunk. The coronary vein drains the venous circulation of the lesser gastric curvature into the proximal portal vein. The gastroduodenal vein collects drainage from the area of the pancreatic head.

Total portal venous flow in a normal man ranges between 600 and 1200ml/min, as measured intraoperatively and by Doppler flowmetry.

The volume of portal flow is regulated by the vascular resistance of the splanchnic arteries[17]. Changes in portal inflow result from modifications in splanchnic arteriolar resistance, as seen with physiologic events such as a change in posture or in the postprandial state. The increase in portal blood flow after a meal can be prevented by pre-administration of somatostatin, an inhibitor of the release of several gastrointestinal hormones that may mediate the arteriolar vasodilatation that occurs after feeding. Portal venous oxygen content decreases after a meal because of increased intestinal arteriovenous extraction of oxygen.

Hemodynamics in Portal Hypertension

Vascular Resistance

Theoretically, a rise in portal pressure could stem from an increase in either portal flow or vascular resistance. Under normal conditions, a rise in portal flow can be accommodated by the compliant hepatic sinusoidal bed so that portal pressure increases only in extreme conditions. For example, although splenic

flow increases markedly in the presence of massive splenomegaly, the critical threshold in the portal flow-pressure relationship is not reached and portal flow-pressure relationship is not reached and portal hypertension does not develop unless increased vascular resistance is also present. This hemodynamic combination can be seen in conditions with splenomegaly, such as Felty's syndrome, sarcoidosis, or lymphomas. An exception is portal hypertension caused by a high portal flow from an arteriovenous fistula, as with splenic artery splenic vein communications, where the flow-volume relation exceeds a critical threshold.

The genesis of portal hypertension involves an increase in portal vascular resistance and is the basis for its classification. Insight into the location of vascular resistance in human cirrhosis has been provided by combined hepatic vein and portal pressure measurements[18]. Most measurements in nonalcoholic cirrhosis show a higher portal venous pressure than hepatic venous wedge pressure, an estimate of sinusoidal pressure. This indicates the presence of a presinusoidal component, probably related to inflammatory activity or fibrotic changes in the portal triads. In alcoholic cirrhosis, the vascular resistance must reside at the level of the sinusoids because portal and hepatic venous wedge pressures are similar.

The pathogenesis of the increased sinusoidal resistance in alcoholic cirrhosis is controversial. The concept of a pathogenic role for the architectural rearrangement and development of fibrotic septa in cirrhosis has been replaced by an emphasis on sinusoidal events. Hepatocyte enlargement, resulting from an alcohol-induced accumulation of fat and protein, may compress the liver sinusoids and obstruct portal flow.

Studies of precirrhotic portal hypertension in baboons chronically fed alcohol have suggested that the degree of perivenular and pericellular fibrosis induced by alcohol correlates with in vivo measurements of portal pressure. This further implicates the hepatic sinusoids as the site of increased vascular resistance in alcoholic cirrhosis. Capillarization of these low-resistance channels, with loss of sinusoidal fenestrae, appearance of collagen in the space of Disse, and the presence of contractile myofibroblasts, may contribute to the development of increased sinusoidal resistance.

A relation between hepatocyte size and intrahepatic pressure in alcoholic liver disease was found for only mild to moderate pressure elevations, although the accuracy of intrahepatic pressure measurements has not been confirmed by others. In nonalcoholic cirrhosis, a more complex relation exists between these parameters.

Portal blood flow and the systemic circulation

Two models have been proposed to explain the alternations of portal flow in response to portal hypertension: the "backward" and "forward" flow hypotheses. The first is based on a rise in portal venous pressure triggering a myogenic response that reduces splanchnic arterial inflow. As a net result, portal pressure values drift back toward normal. If the splanchnic circulation is considered as 2 organs in series (the gastrointestinal tree and the liver), the backward flow hypothesis predicts that inflow into the gastrointestinal tree would be reduced as a result of this rise in portal venous pressure. Even when portal hypertension is fully established, the backward component contributes to its maintenance.

The forward flow hypothesis, in which portal venous inflow is increased, is based on observations in several experimental models and patients. This paradoxical increase in portal venous inflow contributes to the maintenance of portal hypertension. As a hemodynamic syndrome, portal hypertension is unique in exhibiting both increased inflow and increased resistance.

The increase in portal inflow occurs as part of a more generalised hemodynamic disturbance, the `hyperdynamic" circulation. This is characterized by peripheral vasodilatation, a reduction in peripheral vascular resistance, and an increase in plasma volume. As a result, cardiac output and heart rate increase. Decreases in splanchnic and muscular arterial resistance are the main factors contributing to the decrease in systemic vascular resistance. Variable effects are seen on the renal circulation, in which compensatory mechanisms such as renal sympathetic nerve activity, renin-angiotensin, and circulating catecholamines may induce renal vasoconstriction in spite of a decreased peripheral vascular resistance.

The hyperdynamic circulatory state is seen in many forms of portal hypertension. Humoral factors may be responsible for the development of peripheral vasodilatation. Glucagon levels are elevated in the presence of portal hypertension and portosystemic shunts. Other postulated humoral factors include prostacyclin, prostaglandins, bile salts and endotoxin mediated activation of nitric oxide.

PORTAL HYPERTENSION AS A HEMODYNAMIC SYNDROME

Splanchnic hemodynamics

- Increased portal vascular resistance
- Increased portal venous inflow
- Portosystemic shunting

Systemic hemodynamics

- Arterial vasodilatation
- Increased plasma volume
- Decreased systemic vascular resistance
- Increase in cardiac output
- Reduction in mean arterial pressure
- Rise in heart rate

Regional blood flows

- Increased muscle blood flow
- Decreased cerebral blood flow
- Variable renal blood flow

A sequence of events that leads to the hyperdynamic state has been proposed. Although the primary pathophysiologic event is arterial vasodilation, a hyperdynamic state would not develop unless sodium was retained by the kidney, a process mediated by the activation of compensatory mechanisms triggered by the same vasodilatation. Plasma volume is then expanded, which triggers a further decrease in peripheral vascular resistance.

Collateral circulation

When portal pressure reaches a critical value, porto-systemic collaterals may develop. In alcoholic cirrhosis, a corrected portal pressure of 10 to 12mm Hg appears to be necessary for the development of oesophageal varices[19]. These collaterals represent the opening of embryonic channels or redirection of flow within existing veins, rather than the formation of new blood vessels.

Five main pathways of portosystemic collaterals exist

1. Opening of the umbilical vein
2. Reversal of flow in the coronary vein, feeding the development of oesophageal varices.
3. Short gastric veins arise from the splenic vein feeding the gastric varices.
4. Splenorenal collaterals
5. Reversal of flow in the inferior mesenteric vein, feeding the development of anorectal varices.

Alternations in the volume of blood flow may also induce changes in the vascular resistance of the collateral bed. A rise in flow increases vessel diameter and a reduction of flow results in opposite changes, with a smaller vessel offering an increased resistance to flow. The resistance to flow of a fluid in a nondistensible vessel is related to the length of the vessel (1) and the fluid's viscosity (n) and is inversely related to the further power of the radius (r), so that minor changes in vessel diameter markedly affect resistance to flow (Poiseuille's law).

$$\text{Resistance} = 8nl\pi r^4$$

Most pharmacologic agents used for the treatment of portal hypertension reduce portal pressure by reducing portal blood flow. The relation between vessel radius and vessel flow that has been delineated indicates that a reduction in flow may cause a rise in vascular resistance. This is an important principle in the pharmacologic treatment of portal hypertension.

Rupture of oesophageal varices

The mechanisms for the rupture of oesophageal varices have not been fully elucidated. The "corrosion" hypothesis postulated that reflux of gastric acid injured the mucosa of the lower part of the oesophagus with subsequent erosion into the submucosal varies. However, measurements of lower sphincter pressure and pH in the lower oesophagus failed to show evidence of increased gastroesophageal reflux in patients with bleeding oesophageal varices. Attention has shifted to the "explosion" theory, in which oesophageal wall tension reaches a critical level and rupture occurs.

Wall tension in a system of artificial varices is related to the intraluminal pressure and the vessel's radius and is inversely related to its wall thickness. Laplace's law states that a vessel's radius plays a major role in wall tension, providing a physical basis for the clinical observation that large varices[20] and those at a higher pressure are more prone to bleed. Measurements of oesophageal wall thickness, the third element in this equation, cannot be made with current technology but may be of importance when they are available. A relation between variceal pressure and the risk of hemorrhage has been studied by measuring variceal pressure by means of an endoscopic capsule[21]. Patients who bled from varices had a considerably higher pressure than non bleeding patients with cirrhosis and oesophageal varices.

High portal pressures can arise from common daily activities. Elevation of portal pressure to values greater than 100mm Hg has been observed during the Valsalva maneuver. Administration of an anticholinergic can also increase variceal size. The genesis of variceal rupture may be related to daily events in which pressure rises abruptly to extremely high values[22].

Influences of Portal Hypertension on Other organs

Hypersplenism may occur in the absence of splenomegaly. Alterations of the splenic microcirculation, with fibrotic changes in the splenic sinusoids, favor entrapment of red cells, white cells (especially polymorphonuclear leukocytes), and platelets. However, the bone marrow remains active, and infection or bleeding seldom results from leukopenia or thrombocytopenia, respectively. In the absence of other factors that affect the platelet count (alcohol, medications), thrombocytopenia, between 50,000 and 125,000 platelets/nm^3 is an indicator of portal hypertension in cirrhosis.

Hypoxemia, with an arterial partial pressure of oxygen between 60 and 80mm Hg, is a common finding in established portal hypertension. Administration of 100% oxygen does not correct the hypoxemia, suggesting that functional pulmonary arteriovenous shunting is the basic defect. Anatomic connections have been demonstrated on the pleural surface and termed lung "spiders". Vasodilatation of pulmonary capillaries, as part of the generalised process of systemic vasodilatation may increase the distance for oxygen diffusion between the blood and alveolus, resulting in functional shunt. The degree of hypoxemia can be severe.

Pulmonary hypertension develops in a few patients, regardless of the etiology of portal hypertension. The pathophysiology is unclear. Histologic studies do not suggest microscopic pulmonary embolism as a possibility. Rather, vasoactive substances arising from the splanchnic territory, which now by pass the liver, may induce permanent changes in the pulmonary vasculature. Serotonin, thought to be elevated in these patients, is of particular interest as it has been implicated in the pathogenesis of pulmonary hypertension associated with the carcinoid syndrome.

CLASSIFICATION OF PORTAL HYPERTENSION

A logical classification of portal hypertension is based on the site of increased resistance to portal flow. Five main groups can be delineated according to presinusoidal, sinusoidal, or postsinusoidal block. Presinusoidal and postsinusoidal portal hypertension can be further subdivided into intra-or extrahepatic causes. Although the differential diagnosis is extensive, liver cirrhosis is the leading cause of portal hypertension in the West.

Presinusoidal Prehepatic

Presinusoidal prehepatic portal hypertension is most commonly due to portal vein thrombosis. A blood clot in the portal vein can have several causes; however, a definitive diagnosis cannot be made for many patients. Many of these idiopathic cases may represent an early manifestation of a myeloproliferative syndrome. When the colony-forming units were quantitated after bone marrow culture, a diagnostic criterion for myeloproliferative syndrome, many patients with idiopathic portal hypertension met criteria for the diagnosis of this hematologic disorder.

Catheterization of the umbilical vein in newborns has been associated with the development of omphalitis with secondary portal vein thrombosis. Over the years, bridging collaterals develop toward the liver, resulting in a "cavernous" appearance of the portal vein. The prognosis is relatively good because these patients have normal liver function, variceal hemorrhage is better tolerated, and the incidence of bleeding decreases after the second decade.

Disorders of the coagulation system may present as portal vein thrombosis. These include congenital deficiencies of natural anticoagulants such as deficiency of antithrombin III, protein C, protein S, and plasminogen activator. An acquired lupus anticoagulant may also predispose patients to this thrombotic event.

Diseases of the adjacent organs may also cause portal vein thrombi. Invasion into the portal vein by carcinoma of the head of the pancreas or common

bile duct denotes inoperability; carcinomas of the pancreatic body and tail affect the splenic vein. Cirrhosis has been viewed as predisposing to portal vein thrombosis because of stasis.

Classification of portal hypertension

Presinusoidal portal hypertension

Extrahepatic

Portal vein thrombosis

Intrahepatic

Schistosomiasis (S.mansoni, S.japonica)

Sarcoidosis

Felty's syndrome

Arsenic poisoning

Idiopathic portal hypertension

Congenital hepatic fibrosis

Primary biliary cirrhosis

Sinusoidal portal hypertension

Alcoholic cirrhosis

Vitamin A intoxication

Renal transplantation

Nodular regenerative hyperplasia

Postsinusoidal portal hypertension

Intrahepatic

Veno-occulsive disease

Senecio alkaloids

Alcoholic hepatitis (venular sclerosis type)

Extrahepatic

Budd-Chiari syndrome

Congenital web

Splenic vein thrombosis may give rise to gastric varices with hemorrhage. If the liver is normal, the gastric varices drain toward the liver through the coronary vein and esophageal varices may be absent. Chronic pancreatitis and many of the previously discerned disorders that cause portal vein thrombosis may also give rise to this segmental abnormality.

Presinusoidal intrahepatic

A wide range of disorders are included in this category, but portal venule obstruction is the common link. It can occur as a result of vascular obliteration (non cirrhotic portal fibrosis) or as a result of inflammatory activity in the portal triad (early stage of primary biliary cirrhosis, lymphoma) that impinges on the portal venule system.

Schistosomiasis is the most common entity in this group. Eggs shed by the parasite into the splanchnic venous tributaries lodge in the portal vein radicles within the liver. A granulomatous, fibrotic reaction develops around the eggs of

either Schistosoma mansoni or Schistosoma japonicum, obstructing portal venous flow. As a result, prominent hepatomegaly can be detected. Splenomegaly and portosystemic collaterals arise as a consequences of portal hypertension. With progression of the disease, cirrhotic changes may develop, resulting in an additional component of sinusoidal resistance to portal flow.

Noncirrhotic portal fibrosis (idiopathic portal hypertension) is a common cause of portal hypertension in Asia. Obliteration of small portal venules is its characteristic feature and liver function is preserved. Noncirrhotic portal fibrosis can be reproduced in experimental animals by injection of inactivated Escherichia coli into the portal vein, this implies that enteric infection is a possible cause. Arsenic poisoning may also present with presinusoidal features.

Inflammatory infiltration of the portal triads coexists with splenomegaly in another group of disorders. Examples include Felty's syndrome, lymphoma, and sarcoidosis. Several chronic hepatic disorders have a presinusoidal component of portal hypertension; these include nonalcoholic cirrhosis and primary biliary cirrhosis. Congenital hepatic fibrosis may appear with portal hypertension as its initial manifestation.

Sinusoidal

Sinusoidal portal hypertension is the characteristic feature of alcoholic liver disease. Hepatitis B-related cirrhosis has also been reported to involve a sinusoidal resistance site.

Perisinusoidal fibrosis with portal hypertension can be seen with vitamin A intoxication and after renal transplantation. In the latter, azathioprine may be involved in its genesis. Endothelial damage can also be caused by other compounds with thiol groups.

Classified within this group is nodular regenerative hyperplasia. The nodules in this entity are delineated not by fibrous tissue but by collapsed liver parenchymal cells. Mainly reported in patients with rheumatoid arthritis, it has been described in a wide variety of disorders, including myeloproliferative disorders, lymphoma, macroglobulinemia, and myeloma. Occlusion of small portal venules may be the primary disorder that leads to collapse of the reticulin framework and the appearance of nodules not surrounded by fibrous tissue. Partial nodular transformation, with nodularity confined to the area of the hepatic hilum, may be a variant of this disorder.

Postsinusoidal

This can occur within or outside the liver. Most of the these entities present with ascites as the main manifestation of portal hypertension.

Primary increase in Portal Venous inflow

Apart from the classification described earlier, increased portal venous inflow is a rare event that occurs with a direct communication of a splanchnic artery to the portal venous system. Examples include a traumatic arteriovenous fistula arising from the splenic artery and rupture of an aneurysm of the hepatic artery into the portal vein. Aneurysms of the splenic artery are seen in the

presence of splenomegaly and portal hypertension. They arise as a consequence of increased splenic flow and are small, can be multiple, and seldom cause complications.

INVESTIGATION OF THE PORTAL HYPERTENSIVE STATE

Physical Examination

A full clinical evaluation of patients with portal hypertension should include elucidation of the cause, evaluation of hepatic function, and screening for complications. The physical examination may provide special clues to the differential diagnosis.

When patients present with variceal bleeding, cirrhosis cannot be assumed to be present and presinusoidal causes should be considered. However, when patients with portal hypertension also exhibit ascites, a presinusoidal etiology is unlikely unless severe hypoalbuminemia alters the relation between hydrostatic and oncotic pressure in the intestinal capillaries. Cirrhosis may eventually develop in schistosomiasis, and ascites may result from sinusoidal portal hypertension.

Liver size may offer clinical clues. A small liver in the presence of portal hypertension is suggestive of cirrhosis. The consistency of the liver edge can provide additional information, because a normal edge argues against a sinusoidal etiology. The detection of a hepatic bruit may suggest primary carcinoma presenting with variceal bleeding as its initial manifestation. A venous hum in the periumbilical area indicates high flow through a patent umbilical vein, excluding portal vein thrombosis as a cause.

The appearance of a common ailment such as hemorrhoids can seldom be interpreted as an initial sign of portal hypertension. However, proctoscopic examination may reveal additional signs, such as the presence of rectal varies.

Conventional Radiology

A chest radiography may show an enlarged azygos vein appearing as a mass in the right hilar region or enlarged pulmonary arteries when pulmonary hypertension is associated with portal hypertension. Fundico antral varices may be misinterpreted as mass lesions on upper gastrointestinal radiographs.

Angiography of mesenteric vessels provides anatomic information and some functional data. Splenoportography offers the best anatomic detail but has seldom been used because of concern about splenic puncture. Small-gauge needles may be safe when optimal imaging is needed. Venous phases of arterial injections can be enhanced with subtraction techniques, giving better anatomic detail.

Computed tomography with injection of a contrast agent not only images the splanchnic vessels but also provides information about possible liver disease as well as the status of the hepatic veins. Thrombosis of splanchnic vessels can easily be visualized. Similar concepts extend to real-time ultrasonography with Doppler scanning, which can provide accurate determination of the portal flow direction. Hepatofugal flow, described in 8% of patients with cirrhosis, can give rise to an angiographic "pseudothrombosis" image of the portal vein, because contrast material injected into the splenic artery flows toward the variceal collaterals without visualization of the portal vein. Current noninvasive imaging techniques rapidly exclude the presence of a thrombus.

MEASUREMENT OF PORTAL PRESSURE

Direct measurements of portal venous pressure can be obtained by direct puncture of portal tributaries or of venules within the liver. Splenic pulp pressure, measured at the time of splenoportography, may accurately reflect portal venous pressure but is associated with risk of hemorrhage from the puncture site. Catheterization of the umbilical vein, has been re-evaluated with use of the Doppler technique. Percutaneous transhepatic measurements of portal pressure can be obtained at the time of portography. Direct measurements in portal tributaries can also be made at the time of surgery.

All these techniques require an additional measurement of hepatic venous pressure to evaluate the pressure gradient across the liver. Also, organ puncture can occur in patients with liver disease and coagulopathy. The alternative is to approach the liver by way of the hepatic vein. During hepatic venous catheterization, the catheter is maximally advanced and the vein occluded so that a sinusoidal pattern can be seen during injection of dye. Value at this point reflect hepatic venous wedge pressure under normal conditions. Withdrawal of the catheter into the hepatic vein allows estimation of hepatic venous free pressure. Use of the balloon catheter allows measurements of free and wedge pressure from one position in the hepatic vein.

Accurate measurements require adequate calibration of pressure transducers because the range of normal venous pressure values is narrow. An accurate tracing can be identified by its normal respiratory variation and stable values; digital readout of pressure values is unacceptable. Permanent records of such tracings should be incorporated in the patient's chart.

When the etiology of portal hypertension is unclear, pressure measured by hepatic venous catheterization can provide useful clinical information. A low hepatic venous pressure gradient in the presence of oesophageal varices, strongly argues for a presinusoidal etiology. This is the hemodynamic pattern in early hepatic schistosomiasis. A high pressure gradient confirms the presence of parenchymal liver disease, but diagnosing its etiology requires additional testing. Percutaneous transhepatic measurements are useful in the diagnosis of the Budd - Chiari syndrome.

Measurements of pressure are important when therapeutic measures are planned. During surgery to relieve portal hypertension, evidence of adequate decompression is provided by intraoperative pressure measurements. The success of transjugular intrahepatic portosystemic shunt (TIPSS), a nonsurgical technique in which a metallic stent is placed between the portal and hepatic veins, can be measured by the reduction of portal pressure. When considering pharmacologic therapy with beta - adrenergic blockers, reduction of the portal venous pressure gradient to critical levels decreases the occurrence of gastrointestinal hemorrhage.

MEASUREMENT OF BLOOD FLOW

Portal Venous Flow

Measurement of portal blood flow had been considered inaccessible in the nonsurgical setting, but the use of Doppler flowmetry has allowed estimation of portal flow. With this technique, portal mean velocity is measured with the Doppler signal in the middle of the vessel. Flow is obtained by multiplying an

estimate of the cross-sectional area of the portal vein (from the ultrasonographic image) by the calculated mean velocity. The technique can also be used for measurement of arterial inflow, which permits estimation of arteriolar resistance. Doppler flowmetry has also been used to assess the effects on portal hypertension of histologic events, such as feeding, and the responses to pharmacologic agents. A diminished response of portal vessels to respiration may signal a critical reduction in compliance.

Numerous technical problems may interfere with the accuracy of Doppler measurements. These include body habitus, the extent of collateralization (Portal vein flow may be markedly decreased with high collateral flow), and respiratory variations. Intra and interobserver variability in measurements of flow and velocity is considerable. Doppler flowmetry is best suited for comparison within the same subject rather than between groups. Nonetheless, its noninvasive nature is attractive.

Azygos Venous Flow

Under normal conditions, the azygos vein drains blood from the abdomen and lower extremities. With markedly increased flow in portal hypertension, oesophageal varices drain into the azygos and homozygous veins, allowing easy identification of the flow during catheterization. With the continuous thermodilution technique, mean azygos flow was 150 ml min in control subjects; in patients with cirrhosis and portal hypertension, the mean value was 550 ml / min, with wide variation of results. This increase in azygos flow may not solely reflect increased collateral blood flow because drainage from the lower

extremities also contributes to azygos flow. However, bile acid concentration and oxygen tension are higher in the azygos vein of patients with cirrhosis, reflecting the contribution of portal venous blood to this flow.

Measurement of azygos blood flow is useful for indirect estimation of collateral blood flow. Its use, however, has been restricted to research laboratories and has not been extended to standard clinical practice.

MEASUREMENT OF VARICEAL PRESSURE

Measurement of intravariceal pressure by puncture of oesophagal varices before sclerotherapy has been reported. Although initial reports suggested identical values for intravariceal pressure and portal pressure, more accurate measurements indicated a lower value for the former, because pressure is dissipated over a larger vascular bed.

When the sclerotherapy needle is introduced into the varix, it can cross the varix and its tip lies in the muscle layer. A manometric capsule has been used to measure variceal pressure indirectly. It is mounted on an endoscope and positioned over a variceal column. The pressure that obliterates the varix is equivalent to the intraluminal pressure and is recorded with its respiratory variation. This technique has been used to measure variceal wall tension by multiplying the apparent diameter of the varix by the recorded variceal pressure. With these parameters, wall tension was considerably higher in patients who had bled from varices than in non-bleeders.

Quantification of Portosystemic Shunts

Measurement of the degree of portosystemic shunting is not easily attainable in patients. A qualitative assessment can be made by instillation of thallium locally in the upper rectum, in the presence of portosystemic shunts, some of the thallium escapes hepatic uptake and lodges in the heart. By scanning the liver and heart, the presence of portosystemic shunts can be demonstrated in patients with chronic hepatitis, establishing the diagnosis of cirrhosis and portal hypertension.

The bioavailability of drugs given enterally and highly extracted by the liver in their first pass has also been used to measure the extent of portosystemic shunts. Nitroglycerin and sorbitol have been evaluated. The bioavailability of partially infused bile acid was estimated in the same way. However, the intestine also contributes to the first - pass elimination of these drugs. In addition, precision is lost when absorption occurs in intestinal areas that do not belong to the area of collateralization . An accurate and reproducible method is not available.

ENDOSCOPIC SCREENING FOR OESOPHAGEAL VARICES

Endoscopic grading of varices-paqet

Grade I : Small varices without luminal prolapse

Grade II : Moderate-sized varices showing luminal prolapse with minimal obscuring of the gastro-oesophageal junction.

Grade III : Large varices showing luminal prolapse substantially obscuring the gastro oesophageal junction.

Grade IV : Very large varices completely obscuring the gastroesophageal junction.

A major cause of death in patients with cirrhosis is gastrointestinal hemorrhage, most often as a result of the portal hypertensive state[23]. The 1- year bleeding rate of unselected patients with cirrhosis, without a history of hemorrhage, ranges from 6% to 76% and depends on endoscopic features as well as the degree of hepatic decompensation[24]. Mortality for the first variceal hemorrhage ranges from 10% to 65%,[25,26] the majority of deaths occur within the first 6 weeks after the bleeding episode[27]. After variceal bleeding has occurred, life expectancy is dramatically reduced, with a 1 - year survival of 22% to 60%. Patients who die within the first 2 years of their index hemorrhage tend to succumb to variceal bleeding and liver failure; those who survive beyond this period die of other complications.

The prevalence of oesophageal varices on a single endoscopic examination in unselected cirrhotic patients ranges widely. Data on the relation of the presence of varices and variceal size to the degree of liver injury, as measured by the Child- Pugh score, are conflicting. In some cross - sectional studies using the Cox regression analysis, a high Childs, score was predictive of large varices[28]. In others, no direct correlation was found. Varices may be present in patients with child's A cirrhosis and absent in those classified with Child's C disease. On this

basis, all patients with a diagnosis of cirrhosis should be evaluated by upper endoscopy. In one study of patients without varices on an initial examination, 31% and 70% had varices on subsequent examinations at 1 and 2 years, respectively[29].

Barium oesophagograms are good predictors of large varices with a sensitivity of 91%. Radiologic characteristics include scalloping of the oesophageal borders and rounded expansions of the mucosal folds. However, varices must be at least 3 mm for visualization and may often be found to be one grade larger by oesophagoscope than by barium swallow examination. Hiatal hernias make the diagnosis more difficult and gastric fundal varices are difficult to distinguish from gastric folds. Thus, oesophagoscope has been considered the most reliable means of establishing the diagnosis of varices. Fiberoptic oesophagoscope, developed in the 1960s, has led to improved tolerance by patients and greater diagnostic accuracy.

The Japanese Research Society for Portal Hypertension has proposed general rules for recording endoscopic findings of oesophageal varices. In a retrospective analysis, these guidelines were used to establish endoscopic criteria to assess the risk of the first episode of hemorrhage[30]. Those criteria proposed as predictive of variceal bleeding included a serpiginous form, red color markings, and a fundamental blue, color, while esophagitis was not predictive. Prospective studies have confirmed the discriminant function of size and red color signs in predicting the first variceal hemorrhage[31,32]. Although grading systems for estimation of variceal size differ and have not been completely standardized, an

endoscopic evaluation should include assessment of diameter percentage lumen occupancy, and a straight or serpiginous form.

Large, serpiginous varices bleed commonly than small, straight vessels; still, varices of any size may rupture. Most studies show no relation of variceal size to intravariceal pressure as determined by needle puncture or the wedged hepatic - inferior vena cava pressure gradient. The size of varices may wax and wane on serial endoscopic studies. Spontaneous regression in size occurs with improvement of the underlying liver injury. If small varices are seen on initial examination, yearly evaluation should be performed. Every 2 years evaluation may be adequate for those without varices on the initial evaluation.

Red color markings include cherry red spots, red wale markings, and hematocystic spots. These represent dilated intraepithelial and subepithelial venous channels on the surface, of and in communication with, the deeper submucosal variceal veins. Red spots correlate with variceal size and are found on 21%, 42%, and 80% of small, medium, and large varices, respectively. The presence of red color signs is not related to Child score. High variceal pressures, however, may be important in their development and they may be markers for the presence of higher portal pressures. Mean intravariceal pressure determined by needle puncture is 40% higher in patients with red color signs. The risk of bleeding is increased 2-fold in the presence of red color signs. The independence of red color signs and variceal size, however has been disputed[33].

The importance of these endoscopic findings is highlighted by the increasing consideration of prophylactic therapy to prevent variceal hemorrhage.

If the prediction of hemorrhage is accurate, prophylactic therapy could be reserved for patients who are at risk of bleeding.

VARICEAL BLEEDING

It is one of the most dangerous complications of portal hypertension. Variceal bleeding occurs from oesophageal varices that are usually located within 3-5 cm of the oesophagogastric junction or from gastric varices. The size of the varices, endoscopic variceal features such as red spots and red stripes, high portal pressure and liver failure are all general factors that predispose to bleeding. Drugs capable of causing mucosal erosion, such as salicylate and other non - steroidal anti - inflammatory drugs (NSAIDs), can also precipitate bleeding. Variceal bleeding is often severe, and recurrent bleeding occurs if preventive treatment is not given. Bleeding from varices at other sites is comparatively uncommon but most often occurs from varices in the rectum or intestinal stomas.

Management of acute variceal bleeding

The priority in acute bleeding from oesophageal varices is to restore the circulation with blood and plasma, not least because shock reduces liver blood flow and causes further deterioration of liver function. Even in patients with known varices, the source of bleeding should always be confirmed by endoscopy because about, 20% of such patients are found to be bleeding from some other lesion, especially acute gastric erosions.

TREATMENT TO STOP OESOPHAGEAL VARICEAL BLEEDING AND TO PREVENT RECURRENT BLEEDING

Local measures

- Sclerotherapy
- Banding
- Balloon tamponade
- Oesophageal transection

Reduction of portal venous pressure

- Somatostatin
- Vasopressin
- Terlipressin

Prevention of recurrent bleeding

- Sclerotherapy/Banding
- Transjugular intrahepatic portosystemic shunt (TIPSS)
- Portosystemic shunt surgery
- Propranolol

Primary prophylaxis of initial variceal bleeding

In view of the mortality and morbidity associated with variceal hemorrhage, portosystemic shunts, sclerotherapy and propranolol have all been used to try to prevent initial bleeding from varices. Propranolol in a dose of 80 - 160 mg daily can be used for primary prevention.

ASCITES

Ascites refers to the accumulation of free fluid in the peritoneal cavity and is a complication of portal hypertension.

ASCITIC FLUID ANALYSIS

Abdominal paracentesis with ascitic fluid analysis is the most rapid and cost-effective method of determining the cause of ascites. Under aseptic precautions, a standard 1.5 inches needle (22 gauge) is inserted below the percussed air-fluid interface and about (50-100ml) fluid is aspirated for analysis. The fluid is analysed for protein, content, sugar, cell count, cytology, gram's stain and culture.

SERUM ASCITES-ALBUMIN GRADIENT (SAAG)

Ascitic fluid protein concentration is almost entirely dependent on serum protein concentration (direct relationship) and portal pressure (inverse relationship).

The SAAG categorizes ascites better than the total protein concentration. The SAAG correlates with portal pressure. It is physiologically based on oncotic-hydrostatic balance. Portal hypertension results in an abnormally high hydrostatic pressure gradient between the portal bed and ascitic fluid. Albumin exerts more oncotic force per unit weight than other proteins. The difference between serum and ascitic fluid albumin concentration correlates directly with portal pressure[34]. The SAAG is superior to the exudate-transudate concept in the differential diagnosis of ascites[35].

Calculating the SAAG involves measuring the serum albumin concentration and ascitic fluid albumin concentration and subtracting the ascitic fluid from the serum value. The serum values should always be greater. SAAG is not a ratio. If the SAAG is > 1.1 g/dL, the person has portal hypertension with more than 95% accuracy. Conversely if the SAAG < 1.1 g/dL, the patient does not have portal hypertension with more than 95% accuracy. This test is accurate despite ascitic fluid infection, diuresis, therapeutic paracentesis, albumin infusion and etiology of liver disease.

Accuracy of the albumin assay at low albumin concentrations such as 0-1g/dL is important and if not errors occur in calculating SAAG. Another potential problem with the SAAG occurs when the serum and ascitic fluid specimens are not obtained simultaneously.

Another source of inaccuracy occurs when a cirrhotic patient has a serum albumin level <1.1g/dL. The gradient in falsely low in this setting.

COAGULATION ABNORMALITIES IN CIRRHOSIS

A variety of hemostatic disorders have been described in cirrhotic patients. In general, these can be categorized into abnormalities of platelet number or function, increased fibrinolysis, or deficient synthesis of clotting factors.

Cirrhosis is associated with both quantitative and qualitative platelet abnormalities. Approximately 40% of cirrhotic patients have abnormal prolongation of the bleeding time to values of more than 10 minutes and platelet counts less than 100,000[36]/mm^3. The severity of the thrombocytopenia increases with the Child - Pugh classification. This decrease in the number of circulating platelets is related in part to platelet pooling in the spleen caused by portal hypertension and splenomegaly, in part to immunologic destruction of platelets[37], and based on recent studies, in part to diminished hepatic production of thrombopoietin[38].

Several studies have confirmed the presence of platelet - associated IgG in cirrhosis, and immunoglobulin levels increase in proportion to the severity of the liver disease[39]. This is a particular concern in hepatitis C, in which platelet - associated IgG is increased and thrombocytopenia is observed in 41% of patients (as compared with 19% of hepatitis B patients). Hepatitis C may also have direct effects because viral RNA can be detected in circulating platelets. Finally diminished platelet production may play a role in addition to increased platelet sequestration or destruction. Specifically, circulating levels of thrombopoietin, a peptide hormone produced primarily in the liver that stimulates platelet production, are decreased in some patients with cirrhosis and thrombocytopenia.

Cirrhosis is also associated with functional abnormalities when circulating platelet are not activated in a normal manner, resulting in defective clot formation[40]. The decrease in platelet aggregation, as measured by the restitution test, may be related to decreases in glycoprotein Ib levels in the platelet membrane[41] or to defective signal transduction within the platelet. Patients with bleeding times longer than 7 minutes or a clinical history of bleeding have the lowest glycoprotein Ib levels.

Diagnosis

Low platelet counts are commonly associated with physical manifestations of portal hypertension, including ascites and splenomegaly. In general, platelet counts above 70,000/ mm are well tolerated and do not cause prolongation of the bleeding time unless there are associated qualitative platelet abnormalities. Other causes of thrombocytopenia, including diminished production, interferon or other medications, or decreased thrombopoietin), must be excluded by history and bone marrow examination when necessary. Splenic sequestration is most often a diagnosis of exclusion, but increased platelet trapping can be visualized directly using indium tropolone - 111 labeled platelet when uncertainty exists. Platelet associated IgG levels (antiplatelet antibodies) should be measured in most patients, especially those with hepatitis C and autoimmune hepatitis, to assess the possible contribution of immune - mediated platelet destruction. Prolongation of the bleeding can also reflect impaired platelet function. When necessary formal studies of platelet aggregation induced by restitution or other measurements can be performed.

Management

In thrombocytopenia related to portal hypertension and splenic sequestration, there has been limited clinical experience with splenic embolization, aiming to achieve a 40% to 60% reduction in splenic blood flow. Although there is some short - term morbidity with this procedure, it can prolong platelet survival time and decrease the spleen / liver uptake ratio of platelet uptake. In addition, splenic embolization decreases platelet - associated IgG levels, suggesting that the improvement in platelet counts is due not only to effects on splenic pooling but also to immunologic mechanisms.

Transjugular intrahepatic portosystemic shunts represent an attractive approach to treatment of splenic platelet sequestration by lowering portal pressures. However, clinical series are limited in number and do not yet allow definitive conclusions. In a retrospective analysis of 21 patients, there was a significant rise in platelet counts after shunt placement in patients with a postshunt portal pressure gradient less than 12 mm Hg. However, in a larger prospective series, this procedure has no beneficial effect on thrombocytopenia. Thus, transjugular intrahepatic portosystemic shunt cannot be advocated as a treatment for thrombocytopenia.

In view of association between platelet count, spleen size, presence of ascites, child pugh's score etc in patients with cirrhosis with portal hypertension, we tried to correlate the non invasive parameters with endoscopic finding in portal hypertension in an effort to non invasively predict chances of bleed from varices in patients with cirrhosis of the liver.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS 1.0.0.1. Results were expressed as mean ± S.D. Qualitative data were tabulated in frequencies and percentages. Quantitative data were given in mean and standard deviation. Association between qualitative data like sex, childs grade, Ascites, palpable spleen, hepatic encephalopathy and grade of varices were analysed using pearson chi-squared test. Association between qualitative data like Jaundice, Prothrombin time, platelet count, serum albumin, SAAG ratio, spleen size, portal vein diameter and grade of varices were analysed using oneway analysis of variance, (ANOVA) F-test and student t-test. All tests were 2 tailed and a `P' value of $<0.05$ was considered to be significant. `P value <0.001 was considered to be highly significant.

Threshold of different variables for the best compromise sensitivity-specificity was determined using the ROC curve. Then, Multivariate analysis of variables with significant correlation was carried out using stepwise logistic regression analysis.

OBSERVATIONS

The total number of patients in the current study were 72. There were 53 males and 19 females. The Male: Female ratio was 1:0.3. Males formed 73.6% and females 26.4% of the study respectively.

SEX AND VARICES GRADE

Sex	Varices grade			Total
	No varices	Small	Large	
Male	10 (18.9%)	26(49.1%)	17 (32%)	53 (73.6%)
Female	2 (10.5%)	8 (42.1%)	9 (47.4%)	19 (26.4%)

Pearson chi square = 1.63 P = 0.44 (NS)

Of the 53 males, 26 patients (49.1%) had small varices, 17 (32%) had large varices while only 10 (18.9%) had no varices as endoscopy. Among the 19 females in the study 9 of them (47.4%) had large varices while small varices were seen in 8 (42.1%) and no varices at all in only 2 (10.5%). No statistical significance was noted between sex and the presence and grade of varices.

AGE AND VARICES GRADE

Age (Yrs)	Varices grade			Total
	No varices	Small	Large	
31-40	0	3 (8.8%)	2 (7.7%)	5 (6.9%)
41-50	7 (58.3%)	18 (52.9%)	7 (26.9%)	32 (44.4%)
51-60	3 (33.3%)	12 (35.3%)	10 (38.5%)	26 (36.1%)
>60	1 (8.3%)	1 (2.9%)	7 (26.9%)	9 (12.5%)

The majority of patients (80.5%) were in the age group 41-60 years. The mean age of the patients was 51.07 ± 7.57 years, ranging from 32-65 years. Small varices were seen in 18 patients (52.9%) in the age group of 41-50 years and majority of large varices were seen in the 51-60 years age group (38.5%).

MEAN AGE GROUP OF PATIENTS

Varices grade	No. of patients	Mean	Std. Deviation	ANOVA F-test
No varices	12	50.83	5.078	
Small	34	49.41	5.281	F=2.05
Large	26	53.35	10.276	P=0.14
Total	72	51.07	7.574	

P = 0.14 (NS)

The mean age of the patients was highest (53.35 years) for patients with large varices and least (49.41 years) for patients with small varices. `P' value was not significant to suggest correlation between age and varices.

CHILD'S GRADING AND VARICES GRADE

Child's Grade	Varices grade			Total
	No varices	Small	Large	
A	8 (66.7%)	12 (35.3%)	2 (7.7%)	22 (30.6%)
B	4 (33.3%)	18 (52.9%)	8 (30.8%)	30 (41.7%)
C	0	4 (11.8%)	16 (61.5%)	20 (27.8%)

Pearson's chi-square = 28.94 P = 0.001 (significant)

Among the 72 patients studied, 30 patients were in Group B, 22 patients in Group A and 20 patients in Group C. 16 out of 20 patients in Group C had large grade varices (61.5%), while only 4 (11.8%) had small varices. It was noteworthy that all patients in Group C of Childs grading had varices. Small varices were observed in 52.8% (ie) 18 patients in Group B. No varices were seen in 8 (66.7%) of the Group A patients. A statistically significant association was seen between Childs grade C and large grade varices.

ASCITES AND VARICES GRADE

ASCITES	Varices grade			Total
	No varices	Small	Large	
Marked	0	1 (2.9%)	8 (30.8%)	9 (12.5%)
Mild	0	15 (44.1%)	16 (61.5%)	31 (43.1%)
nil	12 (100%)	18 (52.9%)	2 (7.7%)	32 (44.4%)

Pearson's chi-square = 34.95 P = 0.001 (significant)

40 out of 72 patients in the study had Ascites. Mild ascites was noted in 61.5% of patients with large varices, and marked ascites was seen only in 30.8% of patients with large varices. 92.3% of patients with Ascites had varices on endoscopy which was significant.

SAAG RATIO AND VARICES GRADE

Varices grade	N	Mean	Std. Deviation	t-test
Small	16 (40%)	1.327	0.2205	t=1.19
Large	25 (60%)	2.132	2.6918	P=2.42

SAAG ratio calculated for all patients with Ascites showed a mean of 1.33 for small varices and 1.59 for large varices respectively. Student's t-test revealed a significant correlation between a high SAAG ratio and grade of varices.

PALPABLE SPLEEN AND VARICES GRADE

Palpable spleen	Varices grade			Total
	No varices	Small	Large	
Absent	12 (19.%)	34 (53%)	18 (28%)	64 (89.9%)
Present	0	0	8 (100%)	8 (11.1%)

Pearson chisquare = 15.92 P = 0.001 (Significant)

8 out of 72 patients in the study had a palpable spleen, and significantly all of them had large varices on endoscopy. Among the patients in whom spleen was not palpable (89.9%) only 28% had large varices. Univariate analysis showed a significant 'p' value for a palpable spleen.

ENCEPHALOPATHY AND VARICES GRADE

Encephalopathy	Varices grade			Total
	no varices	Small	Large	
Marked	0	1 (2.9%)	3 (11.5%)	4 (5.6%)
Mild	0	5 (14.7%)	13 (50%)	18 (25%)
Nil	12 (100%)	28 (82.4%)	10 (38.5%)	50 (69.4%)

Pearsons chisquare = 19.72 P=0.001 significant

Hepatic encephalopathy was noted in 22 out of 72 patients. Out of 26 patients with large varices 16 patients had encephalopathy (61.5%) and 38.5% of patients with large varices did not have any features of hepatic encephalopathy. Small varices were strongly associated with absence of hepatic encephalopathy (82.4%). All patients who had no varices an endoscopy did not have hepatic encephalopathy.

JAUNDICE AND VARICES GRADE

Serum bilirubin (µmol/L)	VARICES GRADE			Total
	No varices	Small	Large	
<34	1 (8.3%)	6 (17.6%)	4 (15.4%)	11 (15.3%)
34-50	11 (91.7%)	27 (79.4%)	13 (50%)	51 (70.8%)
>50	0	1 (2.9%)	9 (34.6%)	10 (13.9%)

Pearsons chisquare = 15.82 P=0.003 significant

61 out of 72 patients (85%) had jaundice. 51 patients had serum bilirubin in the range of 34-50 µmol/L. The range of serum bilirubin observed in the study was 26-58 µmol/L. Statistical analysis showed a significant `p' value.

MEAN SERUM BILIRUBIN IN THE STUDY GROUP

Varices grade	No. of patients	Mean (µmol/L)	Std. Deviation	ANOVA F-test
No varices	12	36.58	2.937	F=9.75 P=0.001
Small	34	37.21	4.545	
Large	26	43.88	8.892	

The mean value of serum bilirubin for patients with no varices, small and large varices were 36.58 µmol/L, 37.21 µmol/L and 43.88 µmol/L, respectively. An increase in the grade of varices was noted with increasing serum bilirubin levels.

PROTHROMBINTIME AND VARICES GRADE

Prothrombin time (S)	VARICES GRADE			Total
	No varices	Small	Large	
<14	11 (91.7%)	23 (62.6%)	1 (3.8%)	35 (48.6%)
>14	1 (8.3%)	11 (32.4%)	25 (96.2%)	37 (51.4%)

25 out of 37 patients with large varices (96.2%) had a prolonged prothrombin time more than 14 seconds, while 91.7% of patients with no varices had a prothrombin time less than 14 seconds.

MEAN PROTHROMBINTIME(S) IN THE STUDY GROUP

Varices grade	N	Mean(S)	Std. Deviation	ANOVA F-test
No varices	12	14.08	.289	F=24.53 P=0.001
Small	34	14.47	.748	
Large	26	16.50	1.881	

The mean value of prothrombin time was 16.50 seconds for patients with large grade varices on endoscopy. A significant 'p' value was observed.

SERUM ALBUMIN AND VARICES GRADE

Varices grade	N	Mean (g/dL)	Std. Deviation	ANOVA F-test
No varices	12	3.483	0.0389	F=19.5 P=0.001
Small	34	3.306	0.1324	
Large	26	3.058	0.3126	

61 out of 72 patients (85%) had a serum albumin level more than 3 gm/dL, while only 15% had a serum albumin less than 3 mg/dL. The mean value of serum albumin for patients showed a parallel decline with increasing grade of varices. `P' value was significant.

SPLEEN SIZE AND VARICES GRADE

Spleen size (cm)	VARICES GRADE			Total
	No varices	Small	Large	
11 cm	10 (83.3%)	21 (61.8%)	1 (3.8%)	32 (44.4%)
12 cm	2 (16.6%)	13 (38.2%)	12 (46.2%)	27 (37.5%)
13 cm	0	0	8 (30.8%)	8 (11.2%)
14 cm	0	0	5 (19.2%)	5 (7%)

Pearsons chisquare = 15.05 P=0.001 significant

All patients with no varices had a spleen size of 11-12 cm on ultrasonography. Only one patient with large varices had a spleen size of 11cm. Patients with a spleen size more than 13cm were found to have only large grade varices.

PLATELET COUNT AND VARICES GRADE

Platelet count ($x10^3/\mu l$)	VARICES GRADE			Total
	No varices	Small	Large	
<100	1 (8.3%)	8 (23.5%)	21 (80.8%)	30 (41.7%)
100-150	3 (25%)	13 (38%)	4 (15.4%)	20 (27.8%)
>150	8 (66.7%)	13 (38.2%)	1 (3.8%)	22 (30.16%)

Pearsons chisquare = 30.1 P=0.001 significant

The minimum and maximum platelet count in 72 patients were $68x10^3/\mu$ and $296x10^3/\mu L$ respectively. Platelet count of $<100 \times 10^3/\mu L$ was observed in 30 out of 72 patients (41.7%). Among these a significant number of patients 21 (80.8%) had large varices. Only 1 patient with no varices had a platelet count of $<100x10^3/\mu L$. The above observations suggested a strong association between a low platelet count and large varices, and a significant `P' value.

MEAN PLATELET COUNT IN THE STUDY GROUP ($X10^3\mu/L$)

Varices grade	No. of patients	Mean ($X10^3/\mu L$)	Std. Deviation	ANOVA F-test
No varices	12	193.33	64.714	F=18.07 P=0.001
Small	34	154.38	65.236	
Large	26	89.27	27.473	

The mean platelet count of patients with no varices was $193x10^3\mu L$ and small varices $154x10^3\mu L$, respectively. A mean platelet count of $89.27x10^3\mu L$

was observed in patient with large varices. This was statistically significant, as observed by the ANOVA F-test.

PORTAL VEIN DIAMETER AND VARICES GRADE

Portal vein size (cms)	VARICES GRADE			Total
	No varices	Small	Large	
1.1	6 (50%)	12 (35%)	1 (3.8%)	19 (26.4%)
1.2	3 (25%)	11 (32%)	6 (23%)	20 (28%)
1.3	1 (8.3%)	10 (29.4%)	10 (38.5%)	21 (29.2%)
1.4-1.6	2 (16.7%)	1 (2.9%)	9 (35%)	12 (16.7%)

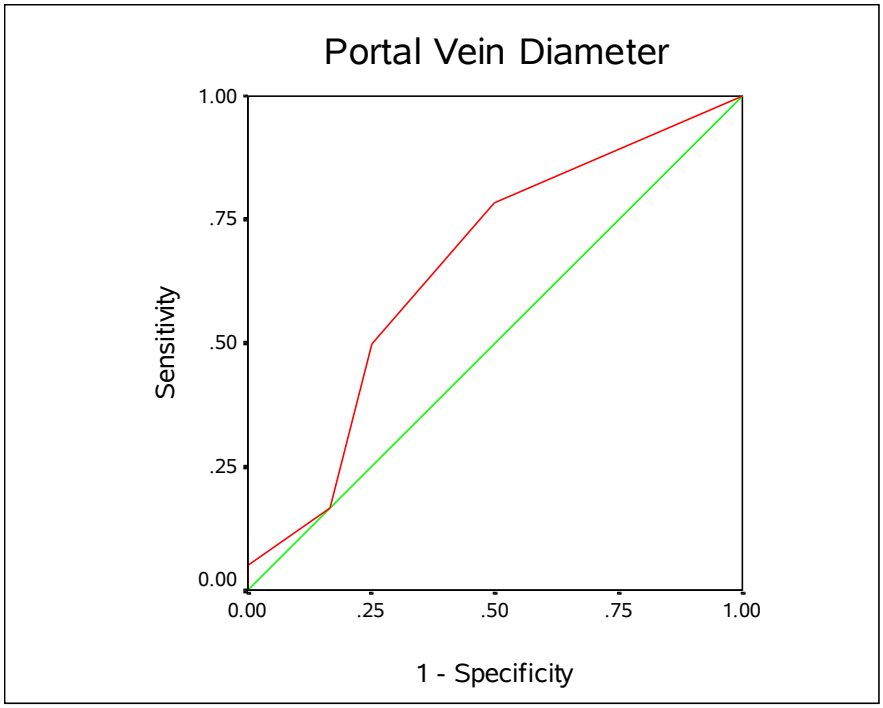
The portal vein diameter an ultrasonogram abdomen in 72 patients ranged from 1.1-1.6cm. In patients with portal vein diameter <1.2cm 75% had no varices, 69% had small varices and only 26.8% had large varices. Large varices were seen in 73.5% of patients with portal vein diameter >1.3cm.

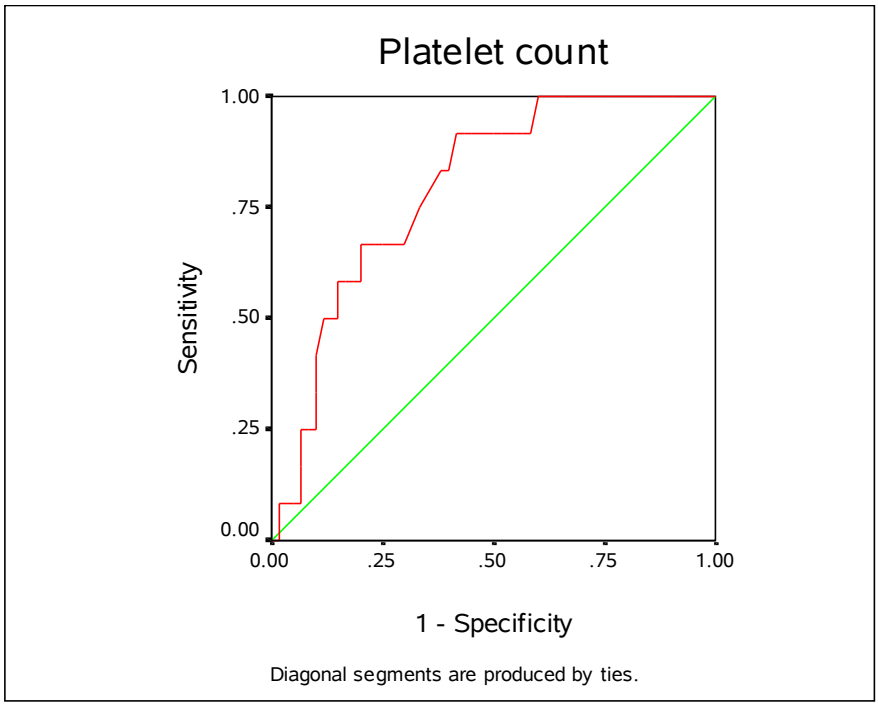
MEAN PORTAL VEIN DIAMETER IN THE STUDY GROUP (cm)

Varices grade	No. of Patients	Mean (cm)	Std. Deviation	ANOVA F-test
No varices	12	1.192	.1165	F=11.67 P=0.001
Small	34	1.200	.0888	
Large	26	1.319	.1132	
Total	72	1.242	.1172	

The mean portal vein diameter in patients with no varices on endoscopy was 1.192 cm compared to 1.2cm in patients with small varices and 1.319 cm in patients with large varices respectively. The ANOVA F-test showed statistical significance.

SENSITIVITY AND SPECIFICITY OF PORTAL VEIN DIAMETER AND PLATELET COUNT





On univariate analysis, significant correlation was noted between the presence of varices and child's grade, ascites, hepatic encephalopathy, palpable spleen, jaundice, serum albumin, prothrombin time, SAAG ratio, platelet count and portal vein diameter. Multivariate analysis of variables with significant correlation was then carried out using stepwise logistic regression analysis.

Parameter	Significance	Odds ratio
Childs grade C	0.046	5.717
Platelet count <90x10^3µL	0.512	2.259
Portal vein diameter >1.15cm	0.532	0.559

Childs grade C, platelet count <90x10^3µL and portal vein diameter >1.15cm showed strong predictive values for the presence of large varices.

The sensitivity and specificity of each of the above parameters was then determined using the ROC curve.

Parameter	Sensitivity	Specificity	Area under curve
Platelet count <90x10^3µL	91%	42%	0.79
Portal vein diameter >1.15cm	78%	50%	0.65
Child's grade C	100%	33%	0.66

The sensitivity of child's grade C was 100% for predicting large varices while it had a poor specificity of only 33%. Platelet count <$90x10^3/\mu L$ had a sensitivity and specificity of 91% and 42% respectively in predicting large varices. Portal vein diameter >1.15 cm had a reasonable sensitivity of 78% and a specificity of 50% for the prediction of large varices. The area under the curve was maximum for platelet count <$90x10^3/\mu L$.

Based on the above observations, a platelet count of <$90x10^3/\mu L$, portal vein diameter >1.15cm and childs grade C were found to have significant predictive value for the presence of high grade varices.

DISCUSSION

Non invasive prediction of oesophageal varices in patients suffering from cirrhosis, with no history of upper GI bleed is essential as the number of patients undergoing screening for the presence of oesophageal varices are likely to increase in the near future, as a result of the growing pool of patients with chronic liver disease.

Multiple studies have been performed to evaluate clinical, laboratory and imaging factors that were strongly associated with the presence of varices.

PLATELET COUNT IN VARIOUS STUDIES PREDICTING OESOPHAGEAL VARICES

Name of study	Year of study	Platelet count
Present study	2004-2006	$<90x10^3/\mu L$
Chalasani et al.[42]	1999	$<88x10^3/\mu L$
Schepis et al.[43]	2001	$<100x10^3/\mu L$
Zaman et al.[44]	1999	$<88x10^3/\mu L$
Sarwar et al.[45]	2003-2004	$<88x10^3/\mu L$
Gill et al.[46]	2004	$<140x10^3/\mu L$

Many studies have been conducted which have shown a low platelet count to be an independent predictor of the presence of large varices. Most of the studies have clearly revealed that a platelet count less than $88x10^3/\mu L$ is associated with large varices an endoscopy. In the present study platelet count of $<90x10^3/\mu L$ showed significant association with the presence of large varices.

PORTAL VEIN DIAMETER IN VARIOUS STUDIES PREDICTING OESOPHAGEAL VARICES

Name of study	Year of study	Portal vein diameter
Present study	2004-2006	>1.15 cm
Schepis et al.[43]	2001	>1.3 cm
Sarwar et al.[45]	2003-2004	>1.1 cm

A very few studies have detailed the portal vein size to be a predictor of large varices. The portal vein size predicting large varices in our study was very similar to that observed in the study by Sarwar et al.

Many of the studies conducted to predict the presence of oesophageal varices non invasively also found significant association with parameters other than portal vein diameter and platelet count.

- Chalasani et al.[42] found that in addition to a platelet count <88x10^3/μL, splenomegaly was independently associated with the presence of large varices.

The present study failed to show any significant association between splenomegaly and presence of large varices.

- Schepis et al.[43] found a prothrombin activity <70%, portal vein diameter >1.3 cm and platelet count <100x10^3/μL significantly associated with oesophageal varices.

The present study showed lesser values for both platelet count and portal vein diameter in detecting oesophageal varices and no strong association between prothrombin time and presence of large varices.

- Zaman et al.[44] found that a platelet count <88x10^3/µL was strongly associated with the presence of oesophageal varices. The present study showed very similar results with only a minor difference of 2x10^3/µL in platelet count.

- Sarwar et al.[45] found that patients with serum albumin <2.95g/dL, platelet count <88x10^3/µL and portal vein diameter >11 mm are more likely to have high grade oesophageal varices an endoscopy.

In our present study results were nearly similar but serum albumin showed no significant association with the presence of large oesophageal varices.

- Gill et al.[46] identified oesophageal varices in 70% cases when surveillance endoscopy was performed only in cirrhosis patients with platelet count <1,40,000/ µL, INR>1.5 and portal vein diameter> 13mm.

Our study results are in variance with the above study.

All the studies have shown an association between a low platelet count and high grade varices on endoscopy.

In the present study, three factors were identified which had an independent association with presence of varices. Childs grade C, platelet count $<90x10^3/\mu L$ and portal vein diameter >1.15cm were significant predictors after multivariate analysis for the presence and grade of oesophageal varices.

Portal vein diameter >1.15cm had significant correlation with high grade varices with sensitivity and specificity of 78% and 50% respectively. Width of portal vein on ultrasonographic examination is an indirect indicator of portal pressure which is responsible for development of varices.

Platelet count $<90x10^3/\mu L$ had significant correlation with high grade varices with sensitivity and specificity of 91% and 42% respectively.

Patients under Childs grade C had a sensitivity and specificity of 100% and 33% respectively in identifying high grade varices.

CONCLUSION

- Platelet count <90x10^3/μL, portal vein diameter >1.15 cm on ultrasonography and childs grade C are independently associated with the presence of high grade varices.

- Patients with established cirrhosis and no past history of upper GI bleed should have surveillance endoscopy if any of these parameters is identified.

SUMMARY

Seventy two patients with cirrhosis of the liver without any previous history of upper GI bleed were studied to identify non endoscopic parameters which could predict the presence of oesophageal varices. Platelet count $<90x10^3/\mu L$, portal vein diameter >1.15cm and childs grade C were found to be independently associated with presence of large varices on endoscopy. Patients with any of these parameters are candidates for surveillance endoscopy.

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PROFORMA

NON ENDOSCOPIC PREDICTORS OF OESOPHAGEAL VARICES IN PATIENTS WITH CIRRHOSIS OF THE LIVER

1. Name
2. Age/Sex:
3. Address:

4. IP No. Date of admission:
5. Occupation:
6. Income:
7. Habits:
   Alcohol
   Smoking
   IV drug abuse/Exposure to CSW
   Month/Year/Hospital of diagnosis of liver disease
   Duration of disease
   Current drugs taken

8. Clinical details (symptom-duration)

   GI Bleed
   Haematemesis
   Malena
   Rectal bleeding
   Ascites
   Jaundice
   Oliguria
   Symptoms of hepatic encephalopathy

9. Comorbid illness (DM/HT/COPD/CVA/Seizures/Others)

10. Clinical examination:

   Pallor

Icterus
Clubbing
Cyanosis
Pedal Edema
KF ring

Vitals

Pulse rate
Blood Pressure
Respiratory rate
JVP

Signs of bleeding skin/nose/gums

CNS examination
CVS
Respiratory system
Abdomen
Free fluid
Splenomegaly

11. Investigations:
Complete Hemogram
Platelet count
BT/CT
Blood sugar
RFT
Urea
Creatinine
Electrolytes
LFT
Total/Direct Bilirubin
ALT
AST
SAP
Total protein

S.Albumin

Ascitic Fluid Analysis

Sugar/Protein
Cell Count
Cytology
Gramstain/AFB
Culture
SAAG ratio

Prothrombin time/INR

Chest X-ray

ECG

UGI Endoscopy
Varices grade
EST

USG abdomen

Portal vein size
Spleen size
Ascites

Viral markers (HBsAg, Anti HCV)

Child's Grading
A/B/C

12. Treatment
Drugs
Sclerotherapy

13. Outcome
Discharge
Death